



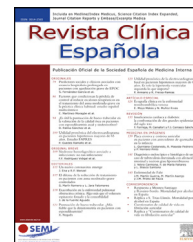
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## REVIEW

## What do we know about the origin of COVID-19 three years later?



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**Abstract** More than three years have passed since the first case of a new coronavirus infection (SARS-CoV-2) in the city of Wuhan (Hubei, China). The Wuhan Institute of Virology was founded in that city in 1956 and the country's first biosafety level 4 laboratory opened within that center in 2015. The coincidence that the first cases of infection emerged in the city where the virology institute's headquarters is located, the failure to 100% identify the virus' RNA in any of the coronaviruses isolated in bats, and the lack of evidence on a possible intermediate animal host in the contagion's transmission make it so that at present, there are doubts about the real origin of SARS-CoV-2. This article will review two theories: SARS-CoV-2 as a virus of zoonotic origin or as a leak from the high-level biosafety laboratory in Wuhan.

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### PALABRAS CLAVE

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**¿Qué sabemos del origen del COVID-19 tres años después?**

**Resumen** Han pasado más de tres años desde el primer caso de infección por un nuevo coronavirus (SARS-CoV-2) en la ciudad de Wuhan (Hubei, China). En esta misma ciudad se fundó en 1956 el Instituto de Virología de Wuhan y en 2015 abrieron en este centro el primer laboratorio de bioseguridad de nivel 4 del país. La coincidencia de ciudad entre los primeros casos de infección y la sede del instituto de virología, sumados a la fallida identificación del RNA del virus al 100% en ninguno de los coronavirus aislados en murciélagos, junto con la falta de evidencia sobre el posible animal intermediario en la transmisión de contagio, hacen que a fecha de hoy surjan dudas sobre el origen real del SARS-CoV-2. En este artículo revisaremos dos teorías, el SARS-CoV-2 como origen zoonótico o como escape del laboratorio de alta bioseguridad en Wuhan.

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## Introduction

Coronaviruses (CoV) are a large group of viruses that usually infect the upper respiratory tract in human beings. They usually produce the clinical condition of a cold, similar to influenza, and appear predominantly in the winter period. The name “coronavirus” refers to the spikes that appear on its surface (projections of proteins from its envelope), which give them the appearance of a stellar corona.<sup>1</sup>

All coronaviruses have a zoonotic origin, that is, they infect different species of animals, giving rise to a respiratory and intestinal infection. There are four genera of CoV: alpha, beta, gamma, and delta. Alpha and beta infect mammals such as bats, cattle, domesticated animals, and humans. Gamma and delta variants most commonly infect birds and other mammals. The first time a CoV was identified as being responsible for a respiratory infection was in 1937; the virus affected poultry and had a devastating effect. In 1965, it was demonstrated that CoV were responsible for approximately 15% to 30% of common colds in humans.<sup>2</sup> But it was not until the beginning of this century when two alerts were received of more severe clinical conditions produced by this family of viruses.

The first alert about more severe symptoms of this infection came in 2002 from the city of Guangdong, in southern China. This infection was named SARS-CoV, with the acronym SARS standing for severe acute respiratory syndrome.<sup>3</sup> It gave rise to very severe clinical conditions and had a mortality rate of around 10%. It infected about 8000 patients in 28 different countries. Ten years later, in 2012, another pandemic outbreak occurred in the Middle East, mainly in Saudi Arabia. It was called MERS-CoV and affected around 2500 people.<sup>4</sup> The acronym MERS stands for Middle Eastern Respiratory Syndrome. Approximately 35% of the patients reported to the WHO died. In the latter case, Saudi Arabia verified that approximately 80% of cases of infection in human beings were the consequence of direct or indirect contact with camels or infected individuals, with the latter largely being healthcare workers. In the case of MERS, close contact with an infected individual was necessary, unlike what later occurred with SARS-CoV-2. These two coronaviruses (SARS-CoV and MERS-CoV) are of the beta genus and are genetically different from one another.

## November 2019

At the end of November 2019, the first case of pneumonia caused by a new CoV, also of the beta genus, was described near the Huanan market, in Wuhan, Hubei province (China). Researchers in China initially named it 2019-nCoV. On February 11, 2020, it was renamed SARS-CoV-2 and the disease was named COVID-19.

As stated above, all CoV that affect human beings have their origin in different animals, which in turn can infect other domestic animals and from there infect human beings. This has been demonstrated through the presence of antibodies in said animals. In the case of SARS-CoV, the horseshoe bat, member of the Rhinolophidae family, was considered the natural host and principal reservoir.<sup>5</sup> In the case of MERS, dromedaries were the principal host.

Therefore, coronavirus disease (COVID-19) is easily transmissible and very contagious from animals to human beings through aerosols, especially in individuals who have been in close contact or shared common spaces, especially enclosed or poorly ventilated spaces.<sup>6</sup>

Initial studies compared the first COVID-19 genome to the bat coronavirus and verified that the sequence was 96.2% identical, a very high percentage but one that does not reach 100%.<sup>7</sup> In addition, what the intermediate host animal could have been has yet to be clearly indicated. In the beginning, the possible intermediate host animal was believed to be pangolin, of the Manidae family, commonly known as pangolins. These mammals are found in tropical areas of Asia and Africa. At present, different studies, including antibody detection, have not been able to demonstrate that this species could have been the intermediate host.<sup>8</sup>

## Wuhan National Biosafety Laboratory in the Zhengdian Scientific Park

In 1956, the Wuhan Microbiology Laboratory was founded under the Chinese Academy of Sciences (CAS). It became the South China Institute of Microbiology in 1961 and was renamed the Wuhan Microbiology Institute in 1962. Later, in 1970, it became the Microbiology Institute of Hubei Province when the Hubei Commission of Science and Technology took control of its administration. Eight years later, it was returned to the CAS and was renamed the Wuhan Institute of Virology. In 2015, the first biosafety level 4 laboratory (the highest existing level) in China opened within this institute. It merits mention that there are only fifty laboratories of this safety level in the world.

Later on, in February 2020, a team led by professor Shi Zhengli at the institute was the first to identify, analyze, and name the genetic sequence of the new coronavirus.<sup>7</sup> The coincidence in the detection of the first cases and the laboratory's presence in that same city has led to a number of authors becoming skeptical of the origins of the pandemic, indicating that the true origin was a “leak” that escaped the strict safety regulations that govern these institutions.

What are these authors' claims based on? First, the viral genome does not coincide 100% with the bat coronavirus,<sup>7</sup> as stated above. Second, the possible intermediate host animal has not been identified. Third, level 4 laboratories tend to work with dangerous pathogens that do not have any available vaccines or treatments. Fourth, these centers investigate animals such as bats and viruses with the potential to trigger future pandemics. Lastly, the laboratories tend to use research techniques that have been a cause of concern in the scientific community for some time. This technique is gain-of-function research,<sup>9</sup> which consists of altering functions through the reverse genetics of a virus in order to comprehensively study it.

Gain-of-function research enhances a pathogen's functions as well as its transmissibility, lethality, or ability to overcome an immune response, vaccines, or medications. It can be used to create new pathogens that do not exist in nature and which pose a risk, as new diseases can be generated either accidentally or deliberately.

In fact, a study published in the journal *Nature* in 2015<sup>10</sup> warned of a possible pandemic in relation with bats. The

aforementioned professor Shi Zhengli, renowned for her field work in bats for predicting and preventing new coronavirus outbreaks participated in the research.

This type of research, conducted by multinational groups of at least fifteen scientists, some of which was conducted in the Wuhan Institute of Virology, sought to prevent future pandemics, develop vaccines, and serve as a foundation for possible treatments. However, it generated a great deal of polemic in the scientific community, which alerted of the danger of creating viral threats. Therefore, there is a possibility that this type of research could give rise to a new version of a virus created from two different coronaviruses, what is known as a chimera virus. And the result could have been a more dangerous version of a virus with a high potential risk.<sup>10</sup>

Adding to the confusion, the Wall Street Journal published an article in May 2021 that stated that three investigators from the Wuhan Institute of Virology had become ill in November 2019 and had symptoms similar to those observed in COVID-19, this just before the pandemic broke out. This again raised even more doubts about the origin of the deadly virus. In that same month of May 2021, eighteen of the most reputable virologists worldwide requested a "detailed investigation" to determine the possible artificial origin of the SARS-CoV-2 coronavirus. In a letter to the prestigious scientific journal *Science*,<sup>11</sup> they requested that its origins be investigated because they could not rule out this possibility, stating, "Theories of accidental release from a lab and zoonotic spillover both remain viable." Notable among the document's signatories are Ralph S. Baric, an important microbiologist at the University of North Carolina. Baric himself was one of the researchers who had previously worked with Shi Zhengli.

Similarly, incidents of virus "escapes" from laboratories have happened in the past, including with SARS-CoV in 2004, which gave rise to a transient chain of transmission. A more well known case is that of the Marburg virus,<sup>12</sup> named after the German city. This virus produces a hemorrhagic disease similar to Ebola and cases were initially limited to Africa. But in 1967 workers in a laboratory in this city close to Frankfurt began to feel ill and have blood coagulation problems. At nearly the same time, in another laboratory in Belgrade, Serbia, people started to report these same symptoms. In total, thirty-one people were affected by a hemorrhagic fever which ended up killing seven of them. What the laboratories in Marburg and Belgrade had in common was work with primates imported from Uganda. It was able to be demonstrated that those affected had come into contact with body fluids and tissues from the animals. The virus was named "Marburg virus disease." Another similar case is the influenza A (H1N1) virus. It is believed that there could have been another "escape" in 1977 from a laboratory that was working to develop a vaccine.<sup>13</sup>

## What happened in Wuhan?

Up until now, as in the plot of a novel, the exposition and climax have been described. Now, the only thing left is the denouement. A definitive conclusion cannot be drawn and more time and research are needed in order to conclusively clarify this matter, if indeed it is possible to do so. Despite

this, data can be provided that could help in determining this future denouement.

On December 27, 2019, at the Hubei Provincial Hospital of Integrated Chinese and Western Medicine (HPHICWM), Dr. Zhang Jixian, head of the respiratory and intensive medicine department, attended to an elderly couple who came in with fever and respiratory distress. Observing large areas of bilateral pneumonia on a lung computed tomography (CT) scan, the doctor insisted that the couple's son, who did not have symptoms, undergo a CT scan. At that time, the same unusual lesions were observed. The couple and their son were the first known cases and the only cases of group transmission up until December 26. They had no known connection to the Huanan market, in Wuhan. Another patient with similar CT scan images, a worker at the Huanan market, was admitted on December 27. Zhang, worried about a new viral disease that was likely infectious, reported the four cases to hospital civil servants, who alerted the Jianghan District Center for Disease Control (CDC) that same day.<sup>7</sup> On December 28 and 29, three more patients, all of whom worked in the Huanan market, were admitted and found to have the same unknown respiratory disease.

A few days before, a similar situation took place in the Central Hospital of Wuhan. On December 18, Dr. Ai Fen, head of the emergency department, encountered the first patient with an unexplainable pneumonia, a 65-year-old man who had gotten sick on December 13 or 15. Though Dr. Fen did not know it at the time, the patient was a delivery person at the Huanan market. A CT scan revealed pneumonia in both lungs that did not respond to the usual treatments. Of the first nineteen cases, there was a clear epidemiological relationship to the Huanan market in twelve.

One of the scientists who has most thoroughly studied the first cases is Professor Michael Worobey, a Canadian evolutionary biologist who is a professor and director of the Ecology and Evolutionary Biology Department at the University of Arizona. He has published several works in high-impact journals, two of which are of note. The first, *Investigate the origins of COVID-19* was published in *Science* in May 2021.<sup>11</sup> This article has been downloaded more than 5.7 million times and cited in more than 2650 scientific articles. The second article, *Dissecting the early COVID-19 cases in Wuhan*<sup>14</sup> was published in that same journal seven months later. In his research,<sup>15</sup> Worobey indicates that the majority of the cases were grouped in the center of Wuhan, close to the western shore of the Yangtze river, with a high density of homes near and around the Huanan market. They used a Kernel Density Estimation (KDE) to reconstruct an underlying probability density function from which the locations of the houses for each case were extracted. This group of cases resided significantly closer to the market than those who worked in it, which seems to indicate that they had been exposed to the virus in the market or close to it. In the case of market workers, the risk of exposure arose from their workplace and not their place of residence, which were significantly farther away than cases not formally linked to the market. Therefore, according to Worobey, "The clustering of COVID-19 cases in December around the Huanan market contrasts with the pattern of widely dispersed cases across Wuhan by early January through mid-February 2020."

In September 2021, other authors such as Holmes et al. also studied the epidemiological relationship of the first

cases and published their findings in the journal *Cell*. They confirmed this epidemiological relationship to the market<sup>16</sup> and did not find a relationship to the geographical location of the Wuhan Institute of Virology, which is located south of the Yangtze river and on the other shore from where the Huanan market is located.

## Do these findings close the discussion on the origins of SARS-CoV-2?

No. As can be seen, there are two theories that could coexist or the debate could be closed by choosing one or the other. Defining chains of infection and seeking the origin of them is a fundamental aspect of public health. Therefore, on the one hand, it seems evident that the transmission originated in the Huanan market. But, on the other hand, three fundamental questions remain that have not been definitively answered. First, where did the virus come from? Second, what was the intermediate animal host? And third, why has the virus genome not been reproduced 100% in any of the coronaviruses found in bats?

More virologic and genomic studies are needed in order to provide a definitive response to these questions, in addition to collaboration from the Chinese government. This fundamental aspect has not occurred throughout the pandemic and it does not seem that it will.

At any rate, two conclusions can be drawn from all of the above. First, respect for nature is fundamental and if we do not control food supply chains, it is possible that new infectious agents that pass from animals to humans will continue to emerge. Second, controls in high safety laboratories are very important and any research study must be subject to the ethical principles of medical practice.

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## Conflicts of interest

The authors declare that they do not have any conflicts of interest.

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